PanAfrican Medical Journal

Open Access

Case series

Oxaliplatin-induced peripheral neuropathy risk factors and management in Tunisian population

Aref Zribi[1], Sonia Ben Nasr[1,&], Syrine Hamdi[1], Jihen Ayari[1], Sana Fendri[1], Mehdi Balti[1], Abderrazek Haddaoui[1]

[1]Faculté de Médecine de Tunis, Department of Medical Oncology, The Military Hospital of Tunis, Universiy of Tunis El Manar, Montfleury, Tunis, Tunisia

[&]Corresponding author: Sonia Ben Nasr, Faculté de Médecine de Tunis, Department of Medical Oncology, The Military Hospital of Tunis, University of Tunis El Manar, Montfleury, Tunis, Tunisia

Key words: Chemotherapy, toxicity, oxaliplatin, neuropathy

Received: 05 Feb 2019 - Accepted: 11 Feb 2020 - Published: 19 Mar 2020

Abstract

The most important limits of oxaliplatin treatment is its peripheral neurotoxicity. The aim of our study was to evaluate the oxaliplatin-induced peripheral neuropathy, its impact on treatment and its management. One hundred chemo-naive patients treated with oxaliplatin-based regimen in the medical oncology department of the military hospital of Tunis between 2012 and 2017 were recruited retrospectively. Evaluation of neuropathy was done according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE V4). Fifty-six patients were aged more than 60 years. The sex-ratio was 1.56. Twenty-seven patients were overweight, 17 were obese and 56 had a BMI inferior to 25 kg/m^2. Two patients were consuming alcohol. Twenty-three patients had diabetes. Sixty-four patients developed chronic peripheral neuropathy because of oxaliplatin (grade 1-2 in 58 cases and grade 3 in 6 cases). Sex, BMI, diabetes and alcohol consumption were not associated with the development of peripheral neuropathy. No association was found between grades of neuropathy and sex, alcohol consumption and diabetes. The median cumulative dose of oxaliplatin that induced neuropathy was 432.4 mg/m^2. The most prescribed treatment was gabapentin (81%) and carbamazepine (16.8%). The treatment was not sufficient to stop neuropathy in 82.6% of cases. Dose reduction was done in 64.2% of cases, treatment delay in 10.7% of cases and treatment interruption in 10.7% of cases. We didn't find any association between known risk factors and peripheral neuropathy. The cumulative dose is interesting to define or to predict the timing of neurotoxicity.

Pan African Medical Journal. 2020;35:83. doi:10.11604/pamj.2020.35.83.18357

This article is available online at: http://www.panafrican-med-journal.com/content/article/35/83/full/

Introduction

Oxaliplatin is a third generation platinum-based agent largely used in oncology. It's effective in the treatment of localized and metastatic gastrointestinal cancers and has improved survival with a 5 year disease free survival of 78% [1-4]. One of the most important limits of oxaliplatin treatment is its peripheral neurotoxicity. Acute and chronic neuropathy differ in their timing, duration and symptomatology. Acute oxaliplatin neurotoxicity is induced by cold and is characterized by distal sensory symptoms such as paresthesia and dysesthesia occurring in days following oxaliplatin infusion [5]. It occurs rapidly in nearly all patients treated and is typically transient [6,7]. The chronic form occurs because of the repetition of chemotherapy (CT) cycles. Neuropathy is cumulative dose-dependent and can persist for months leading to quality of life deterioration [8-10]. Currently, there is no effective strategy for preventing oxaliplatin-induced peripheral neuropathy (OIPN) and pharmacologic management is limited [11]. The aim of our study was to evaluate the OIPN, its impact on treatment and to discuss its management.

Methods

Study population: one hundred and six chemo-naive patients treated in the medical oncology department of the military hospital of Tunis between 2012 and 2017 were recruited retrospectively. We excluded four patients because of allergy to oxaliplatin and two others because of incomplete data. Patients received an oxaliplatin-based regimen: FOLFOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), GEMOX (gemcitabine and oxaliplatin) or XELOX (capecitabine and oxaliplatin). Evaluation of neuropathy was done according to the National Cancer Institute Common Terminology Criteria for Adverse Events: NCI-CTCAE V4.

Data collection: we collected parameters that might be associated with neuropathy according to literature: diabetes, alcohol consumption, body mass index (BMI) and neuropathy treatment.

Statistical analysis: statistical analysis was performed with SPSS software version 20. The comparison between the different variables was made using the khi-2 test for qualitative variables and the T-student test or Anova for quantitative variables. A p-value equal or less than 0.05 was considered statistically significant.

Results

Fifty six patients (56%) were aged more than 60 years. Sex-ratio was 1.56. Twenty seven patients (27%) were overweight (BMI between 25 and 30 kg/m^2), 17 (17%) were obese (BMI superior to 30 kg/m^2) and 56 (56%) had a BMI inferior to 25 kg/m^2. Two patients (2%) were consuming alcohol. Twenty three patients (23%) had diabetes (Table 1). Sixty four patients (64%) developed chronic peripheral neuropathy because of oxaliplatin. Thirty five patients (35%) developed grade 1 toxicity, 23 (23%) developed grade 2 toxicity and 6 (6%) had a grade 3 neuropathy. Sex (38% in male and 26% in female, p=0.656) and body mass index (p=0.082) were not associated with the development of peripheral neuropathy. Diabetes (18% in diabetic and 26% in non-diabetic patients, p=0.970) and alcohol consumption (62% if alcohol consumption and 26% if not, p=0.535) were not associated with neuropathy. No correlation was found between grades of neuropathy and sex, alcohol consumption and diabetes (Table 2). The median cumulative dose of oxaliplatin that induced neuropathy was 432.4 mg/m^2. The most prescribed treatment was gabapentin (81.13%), followed by oxcarbazepine (16.8%). In 82.69% of cases, the medication was not sufficient to stop neuropathy which contributed to dose reduction in 64.2% of cases, treatment delay in 10.7% of cases and treatment interruption in 10.7% of cases.

Discussion

In our population, 64% of patients developed chronic peripheral neuropathy. Berg C *et al.* reported a rate of 71% of neuropathy [12]. According to our study, neither age, sex, alcohol consumption nor BMI were associated to neuropathy. We didn't find any association between known risk factors and OIPN probably because the study was retrospective with a limited number of patients. A study done by Shahriari A *et al.* [13] on patients with colorectal cancer in Iran reported no association between age, sex, alcohol consumption and incidence of neuropathy. Patients with neuropathy had a higher BMI (p=0.003). Incidence of neuropathy was higher if alcohol consumption was ≥5 glasses in a single occasion for men and ≥4 glasses in a single occasion for women, usually within 2 h (p=0.003) [7] and grade 2/3 neurotoxicity occurred more often if

there was high alcohol intake [14]. Diabetes wasn't associated with neuropathy in our study. Uwah AN *et al.* [15] evaluated the relationship between preexisting diabetes and OIPN and found a mean cumulative dose at onset of oxaliplatin regimen of 554 mg/m^2 for all patients with neuropathy, 388 mg/m^2 for patients with diabetes and 610 mg/m^2 for patients without diabetes. Although patients with diabetes developed OIPN at a lower cumulative dose of oxaliplatin, diabetes did not appear to affect the severity of OIPN. Other troubles such as hypomagnesaemia and anemia must be considered as they seem to be associated with peripheral neuropathy. These biological disorders are easily measurable before the initiation of treatment and could predict toxicity.

There is an association between the incidence of neuropathy and hypomagnesaemia and anemia [13]. The cumulative dose is interesting to know to prevent the risk of treatment discontinuation. The chronic form of OIPN is cumulative dose-dependent characterized by distal sensory symptoms causing functional impairment in approximately 15% of cases receiving a 780-850 mg/m^2 cumulative dose of oxaliplatin [8-9]. Berg C *et al.* retained a median warning threshold of 600 mg/m^2. This defined threshold will alert the doctor of the risk of continuing treatment [12]. According to our study, the average cumulative dose that induced neuropathy (all grades included) was 432.4 mg/m^2. The average cumulative dose found in the Tunisian population is inferior to that of other studies done in other populations. Oxaliplatin-induced peripheral neuropathy (OIPN) may vary in frequency and severity among different cancer patients despite equal treatment schedules. A genetic susceptibility for more severe OIPN should be discussed in more researches to investigate the molecular mechanisms of oxaliplatin neurotoxicity. The chronic form of OIPN worsens quality of life and hampers the long-term administration of oxaliplatin, leading to dose reduction, treatment delay or discontinuation of treatment. Neuropathy could be reduced by the use of medication, but in our study only 17% of patients responded to treatment. Argyriou *et al.* conducted a randomized, open-label, controlled trial to assess the efficacy of oxcarbazepine for OIPN treatment.

Thirty-two patients with colon cancer received 12 courses of the FOLFOX-4 regimen and were randomly assigned to receive oxcarbazepine (600mg BID) or CT without oxcarbazepine. The incidence of OIPN was lower with oxcarbazepine (31.2% vs 75%) [16]. Magnowska M *et al.* evaluated the response to gabapentin in a group of patients who developed neuropathy. There was an improvement with gabapentin in symptoms ($p<0.027$), pain ($p<0.027$) and neurologic deficit ($p<0.019$) [17]. Yang *et al.* showed evidence of duloxetine (a balanced selective serotonin (5-HT)) and norepinephrine reuptake inhibitor (SNRI) efficacy in chronic OIPN treatment in patients with colorectal cancer after oxaliplatin-containing CT. Duloxetine effective dose was 60 mg/day [18]. Calcium and magnesium infusion before CT initiation is a routine preventive action. However, its effectiveness remains controversial [19]. A randomized phase III study on 353 patients treated with Folfox showed that there is no statistically significant difference in the incidence of neuropathy between magnesium and calcium infusion and placebo [19], while a retrospective study on 102 patients under FOLFOX regimen, reported that magnesium and calcium infusion decreased the incidence of chronic neuropathy [20]. Balaysac *et al.* demonstrated the preventive effect of a polyamine reduced diet on both acute and chronic OIPN [21]. According to the latest American Society of Clinical Oncology (ASCO) recommendations, infusion of magnesium and calcium solution to prevent neuropathy it is no longer recommended. Use of duloxetine is recommended because of its proven efficacy in many researches [22].

Conclusion

In our study, we didn't find any association between known risk factors and OIPN. The cumulative dose is interesting to define or to predict the timing of neurotoxicity. We may then consider protocol continuation, doses re-estimation or therapeutic alternative, benefit/risk ratio evaluation. Few ways to prevent and limit neurotoxicity are yet available.

What is known about this topic

- OIPN can limit treatment with oxaliplatin;
- The chronic form of OIPN is cumulative dose-dependent, cumulative dose of oxaliplatin reported in the literature was between 600 and 850mg/m^2;
- There are no agents recommended for the prevention of OIPN.

What this study adds

- Our Tunisian population was characterized by a cumulative dose of oxaliplatin inducing OIPN below the dose described in the literature;
- Tunisian patients are more vulnerable to oxaliplatin than other patients probably for genetic reasons;

- OIPN worsens quality of life and disrupts the course of treatment with oxaliplatin.

Competing interests

The authors declare no competing interests.

Authors' contributions

Aref Zribi, Sonia Ben Nasr, Hamdi Syrine, Jihen Ayari and Sana Fendri contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data and drafting the article. Mehdi Balti and Abderrazek Haddaoui contributed to revising the article critically for important intellectual content and final approval of the version to be published. All the authors have read and agreed to the final manuscript.

Acknowledgments

We thank all authors for their contribution to the manuscript's elaboration.

Tables

Table 1: patients characteristics
Table 2: factors associated with neuropathy

References

1. Kalofonos HP, Aravantinos G, Kosmidis P, Papakostas P, Economopoulos T, Dimopoulos M *et al*. Irinotecan or oxaliplatin combined with leucovorin and 5-fluorouracil as first-line treatment in advanced colorectal cancer: a multicenter, randomized, phase II study. Ann Oncol. 2005;16(6):869-877. **PubMed** | **Google Scholar**

2. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK *et al*. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J ClinOncol. 2003;21(11):2059-2069. **PubMed** | **Google Scholar**

3. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T *et al*. Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350(23):2343-2351. **PubMed** | **Google Scholar**

4. Comella P, Lorusso V, Maiorino L, Casaretti R, Cannone M, Massidda B *et al*. Oxaliplatin, irinotecan and fluorouracil/folinic acid in advanced gastric cancer: a multicenter phase II trial of the Southern Italy Cooperative Oncology Group. Cancer Chemother Pharmacol. 2009;64(5):893-899. **PubMed** | **Google Scholar**

5. Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. Ther Clin Risk Manag. 2005;1(4):249-258. **PubMed** | **Google Scholar**

6. Pachman DR, Qin R, Seisler DK, Smith EM, Beutler AS, Ta LE *et al*. Clinical course of oxaliplatin induced neuropathy: results from the randomized phase III trial N08CB (Alliance). J Clin Oncol. 2015;33(30):3416-3422. **PubMed** | **Google Scholar**

7. Beijers AJ, Mols F, Vreugdenhil GA. Systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration. Support Care Cancer. 2014; 22(7): 1999-2007. **PubMed** | **Google Scholar**

8. Gamelin E, Gamelin L, Bossi L, Quasthoff S. Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol. 2002;29(5 Suppl 15):21-33. **PubMed** | **Google Scholar**

9. Grothey A. Clinical management of oxaliplatin associated neurotoxicity. Clin Colorectal Cancer. 2005;5 Suppl 1:S38-S46. **PubMed** | **Google Scholar**

10. Mols F, Beijers T, Lemmens V, Van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association with quality of life among 2 to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. J Clin Oncol. 2013;31(21):2699-2707. **PubMed** | **Google Scholar**

11. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G *et al*. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014;32(18):1941-1967. **PubMed** | **Google Scholar**

12. Berg C, Essner C, Bourderont D, Aujoulat O. Détermination d'un seuil de toxicité neurologique pour l'oxaliplatine. J Clin Pharmacy. 2001;19(4):266-271. **Google Scholar**

13. Shahriari-Ahmadi A, Fahimi A, Payandeh M, Sadeghi M. Prevalence of oxaliplatin-induced chronic neuropathy and influencing factors in patients with colorectal cancer in Iran. Asian Pac J Cancer. 2015;16(17):7603-7606. **PubMed** | **Google Scholar**

14. Vincenzi B, Frezza AM, Schiavon G, Spoto C, Silvestris N, Addeo R *et al*. Identification of clinical predictive factors of oxaliplatin-induced chronic peripherical neuropathy in colorectal cancer patients treated with adjuvant folfox IV. Support Care Cancer. 2013;21(5):1313-1319. **PubMed** | **Google Scholar**

15. Uwah AN, Ackler J, Leighton JC Jr, Pomerantz S, Tester W. The effect of diabetes on oxaliplatin-induced peripheral neuropathy. Clin Colorectal Cancer. 2012;11(4):275-279. **PubMed** | **Google Scholar**

16. Argyriou AA, Chroni E, Polychronopoulos P, Iconomou G, Koutras A, Makatsoris T *et al*. Efficacy of oxcarbazepine for prophylaxis against cumulative oxaliplatin-induced neuropathy. Neurology. 2006;67(12):2253-2255. **PubMed** | **Google Scholar**

17. Magnowska M, Izycka N, Kapola-Czyz J, Romala A, Lorek J, Spaczynski M *et al*. Effectiveness of gabapentin pharmacotherapy in chemotherapy-induced peripheral neuropathy. Ginekol Pol. 2018;89(4):200-4. **PubMed** | **Google Scholar**

18. Yang YH, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK *et al*. Duloxetine improves oxaliplatin-induced neuropathy in patients with colorectal cancer: an open-label pilot study. Support Care Cancer. 2012;20(7):1491-7. **PubMed** | **Google Scholar**

19. Loprinzi CL, Qin R, Dakhil SR, Fehrenbacher L, Flynn KA, Atherton P *et al*. Phase III randomized, placebo-controlled, double blind study of intravenous calcium and magnesium to prevent oxaliplatin-induced sensory neurotoxicity. J ClinOncol. 2014;32(10):997-1005. **PubMed** | **Google Scholar**

20. Grothey A, Nikcevich DA, Sloan JA, Kugler JW, Silberstein PT, Dentchev T *et al*. Intravenous calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in adjuvant colon cancer. J Clin Oncol. 2011;29(4):421-427. **PubMed** | **Google Scholar**

21. Balayssac D, Ferrier J, Pereira B, Gillet B, Pétorin C, Vein J *et al*. Prevention of oxaliplatin-induced peripheral neuropathy by a polyamine-reduced diet-NEUROXAPOL: protocol of a prospective, randomised, controlled, single-blind and monocentric trial. BMJ. 2015;5(4):e007479. **PubMed** | **Google Scholar**

22. Pachman DR, Watson JC, Lustberg MB, Wagner-Johnston ND, Chan A, Broadfield L *et al*. Management options for established chemotherapy-induced peripheral neuropathy. Support Care Cancer. 2014;22(8):2281-95. **PubMed** | **Google Scholar**

Table 1: patients characteristics		
Variables	**Interval**	**Number**
Age	>60 years	56
	≤60 years	44
Sex	Male	61
	Female	39
BMI (kg/m²)	<25	56
	25-30	27
	>30	17
Alcohol consumption	Yes	2
	No	98
Diabetes	Yes	23
	No	77
This table reported the patients characteristics		

Table 2: factors associated with neuropathy				
Variable		**Neuropathy**		**p-value**
		Yes (%)	**No (%)**	
Sex	H	38	23	0.656
	F	26	13	
Alcohol Consumption	Yes	2	0	0.535
	No	62	36	
Diabetes	Yes	18	10	0.970
	No	46	26	
BMI (kg/m²)		27.47±4.91	23.81±3.73	0.082
Age (years)		58.59±10.89	61.86±9.746	0.062
This table reported the risk factors associated with neuropathy				